

THE BRITISH JOURNAL OF DERMATOLOGY

DECEMBER 1955

MEPACRINE AND CHLOROQUINE IN THE TREATMENT OF ROSACEA.

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AFTER mepacrine and later chloroquine proved effective in the treatment of lupus erythematosus which is often provoked by sunlight, it was reasonable to investigate their effect on diseases which can be wholly or partly provoked by light. Good results have been obtained in the treatment of chronic polymorphic light eruptions (Rogers and Finn, 1954; Brodthagen and Christiansen, 1955).

Rosacea is one of the diseases which in some cases may be provoked by sunlight, although cold, wind, heat, and several other factors may aggravate it. In its complex aetiology the psychogenic factor is of the greatest importance (Klaber and Wittkower, 1939). Rosacea primarily affects the blood vessels of the dermis, and has been described by Stokes *et al.* (1942) as a vasomotor neurosis.

The studies to be reported below, started in March 1954, were designed to investigate the value of mepacrine and chloroquine in the treatment of rosacea, regardless of its severity and duration, but with a special view to its possible provocation by light.

MATERIAL AND METHODS.

The material comprises 57 patients ranging in age from 14 to 87, 41 of whom were females and 16 males. The average age was 47 years and the duration of the disease ranged from 6 months to 35 years, averaging 5 years. The series includes quite mild as well as very severe cases, but the great majority were of moderate degree, meaning moderate redness as well as a moderate number of pustules and infiltrations.

The main complaints were itching and burning, especially brought on by fluctuations in temperature and by stormy weather. It is striking, however, that 17 patients had only cosmetic complaints. Twenty-three were certain that exposure to sunlight was a directly provocative factor, and 15 reported seasonal variations. Of the latter 11 were most severely affected in the winter, 3 in the summer, and 2 had exacerbations in both summer and winter.

As criteria of the effect of treatment, the author counted subsidence of infiltrations, pustules, and diffuse redness as well as diminished subjective sensations in the lesion. As telangiectases remain unaffected, they were not included among the criteria.

Of the 57 patients 21 had mepacrine, and the remaining 36 were treated with chloroquine (Avlochlor). A total of 70 courses were completed, 13 patients having 2, in most cases with chloroquine. The dosage was two tablets daily during the first 10 days and then 1 tablet daily for a minimum of 3 weeks (the mepacrine tablets contain 100 mg. and the chloroquine tablets 200 mg.). In the cases treated with mepacrine the maximum treatment period was 10 weeks and the maximum dose 10 g.; the corresponding values for the chloroquine cases were 15 weeks and 28.4 g.

The patients were tested for light tolerance while not under treatment. The minimum erythema dose was determined on the volar aspect of the left forearm. To this end, we used a mercury arc lamp (Hanau) with strong spectral lines of 2970–3020–3120 Å in the most erythemogenic part of the ultraviolet band. No filter was used, and the lamp was adjusted photometrically once a week. The irradiated fields were squares of 1×1 cm., and the irradiation periods 1, 2 and 4 minutes with a lamp-skin distance of 50 cm. Readings were made at the end of 24 hours.

RESULTS.

Of the 57 patients 18 became symptom-free—infiltrations, pustules, and redness disappearing. Telangiectases remained unaffected. An additional 10 patients reported improvement, but did not exhibit objective signs of such improvement. One patient showed objective, but not subjective improvement. A total of 27 patients reported that the sensations in the lesion had diminished or ceased, whereas in one the itching had increased.

Relating the therapeutic result to the reported provocative effect of sunlight, we find that of the 23 patients who reported exacerbation by sunlight 16 improved. Six patients had recurrence 2 to 5 weeks after the treatment was completed; five of these had another course, effective in only one.

Fig. 1 gives the number of cases in the month when treatment was discontinued. It also gives the number who reported a provocative effect of sunlight and the number of cures within this group. At the same time, the figure

shows the monthly hours of sunlight in Copenhagen. In Fig. 2 the number of cases which remained unaffected by the treatment is plotted against the monthly hours of sunlight.

SIDE EFFECTS.

Side effects were most severe and most serious in the group treated with mepacrine. During the 24 courses given 19 patients developed a yellow

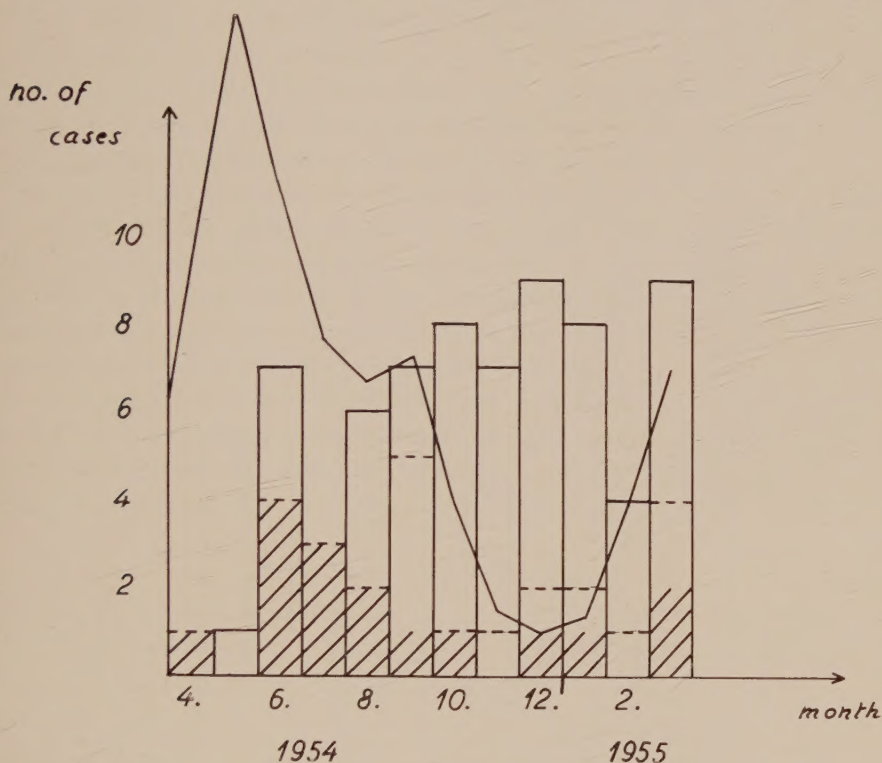


FIG. 1.—Total number of cases in the month when treatment was discontinued. The broken line indicates those in which the disease was provoked by light and the shaded area the cures in this group. The curve gives the hours of sunshine (1:20) in Copenhagen.*

discoloration of the skin and 2 dermatitis of a seborrhoeic type—both at the end of 2 months' treatment. In these cases, the disease was of 5 and more than 7 months' standing respectively.

During the 45 courses of chloroquine, 9 patients developed dyspeptic symptoms, not particularly severe and not necessitating withdrawal of the drug. These symptoms subsided after the treatment was discontinued. One patient had an urticarial eruption with fever of $39^{\circ}\text{C}.$, so that the treatment had to be interrupted. All the patients had systematic determination of the

* Data kindly supplied by the Meteorological Institute of Denmark, Climatological Department.

haemoglobin level, erythrocyte sedimentation rate, red and white blood counts and differential counts. No haematological changes occurred.

The minimum erythema doses are shown in Table I.

TABLE I.—*Minimum Erythema Dose (m.e.d.) Read at the End of 24 Hours.*

m.e.d.	Number of patients.	Solar provocation.	No solar provocation.
>4 min.	6	2	4
4 "	19	8	11
2 "	15	5	10
1 "	10	3	7

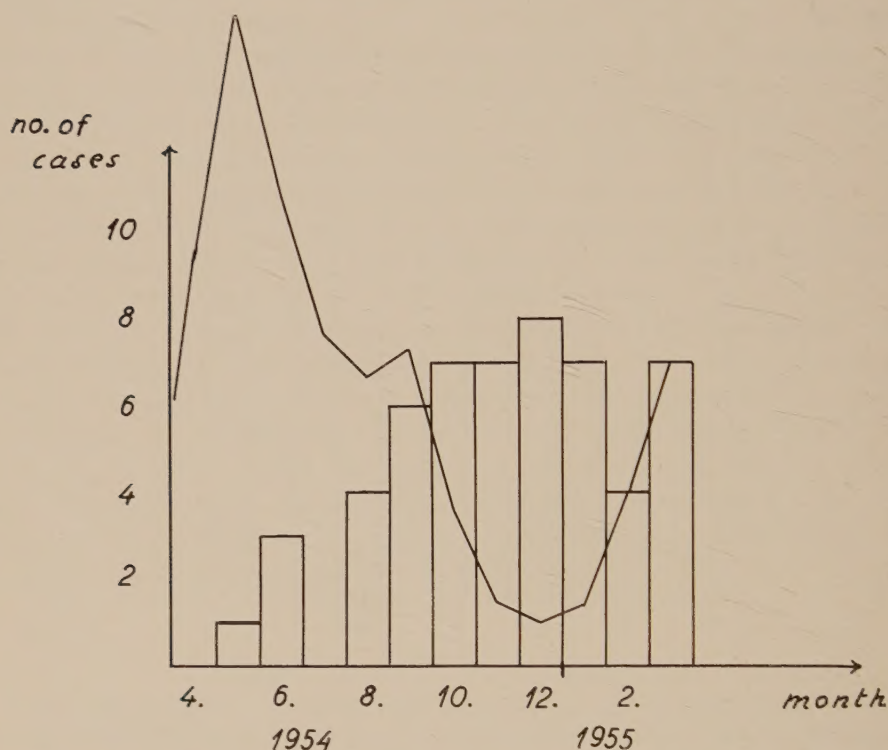


FIG. 2.—Number of cases in which treatment failed in the month when the treatment was discontinued. The curve give the hours of sunlight (1': 20) in Copenhagen.

DISCUSSION.

Since the aetiology of rosacea is probably a complex one, it is difficult to investigate one factor—in this case provocation by sunlight. However, the present study showed that the group of patients who report exposure to sunlight as a provocative factor can be improved or cured by agents which increase the light tolerance. Some patients relapsed when the treatment period was too brief, i.e. did not extend over the period of marked light intensity and many hours of sunlight.

Freedom from symptoms and signs was obtained in 18 of the 57 patients. Sixteen of these were from the group of 23 whose lesions were reported to be provoked by sunlight.

It may be seen from Fig. 1 that the therapeutic effect was observed 1 or 2 months after the many hours of sunlight in May, but this is a result of the method of recording and the duration of the treatment—a minimum of 4 weeks. Fig. 2 shows that the number of patients whose rosacea remained unaffected by the treatment was highest in the months with fewest hours of sunlight and least light intensity.

The dosage was fixed in accordance with experience in the treatment of chronic polymorphic light eruptions in which the effective dose appears to be about 100 mg. of mepacrine or 200 mg. of chloroquine daily.

The side effects correspond to those observed by other workers. There was no case of agranulocytosis or aplastic anaemia (Custer, 1946). The patients were not examined for methaemoglobin, but none of them complained of dyspnoea or striking fatigue during the treatment (Ayres and Ayres, 1955). Chloroquine seems to be preferable to mepacrine because of the yellow discoloration and the risk of dermatitis evidenced in two cases.

In this series, the study of the minimum erythema dose was worthless. It failed to show any relationship between light sensitivity and the provocation of rosacea by sunlight, although the site tested is usually also exposed to sunlight. It also proved impossible to induce rosacea-like affections at the irradiated site.

SUMMARY AND CONCLUSION.

Among 57 patients with rosacea 18 were rendered entirely symptom-free by mepacrine or chloroquine. Sixteen of the cured patients belonged to a group of 23 who had observed that the lesions were provoked by sunlight. The effect was most marked in the months with highest intensity of ultraviolet light and most hours of sunlight. The effect observed in a few other cases presumably represents only spontaneous fluctuations.

It is extremely likely that the effect of mepacrine and chloroquine upon rosacea is due to the capacity of these drugs to increase the light tolerance. Therefore, this treatment should be reserved for cases in which the light provocation has been definitely ascertained by the patient himself, as the susceptibility of the skin to quantitative irradiation does not appear to afford any guidance.

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SKIN HAZARDS OF COAL MINING WITH PARTICULAR REFERENCE TO DERMATITIS.

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ABOUT 780,000 men are employed in coal mines in the United Kingdom ; of these about 45–55% are coal-face workers, 25% on the main roads doing haulage, etc., and 15–20% on the surface.

The figures of incidence of dermatitis quoted in the 1952 report of the Ministry of Pensions and National Insurance give an overall net certification rate of 5·4 per 1000 per annum. The highest rate is 7·4 per 1000 in South Wales and the lowest 2·8 per 1000 in the West Midlands. These great variations may reflect different physical characteristics of pits or perhaps be related to the constitution or morale of the workers.

A rate calculated from the diagnoses on certificates which includes all spells of incapacity may be misleading. Dr. Matthews (1955) by examination of all workers has found the actual incidence at one time to be 8 per 1000 and 4 per 1000 in two pits of 1000 workers each.

The hazards of coal mining seem to be due more to physical conditions of working than to chemical irritation or sensitization. These expose the skin to trauma, coal and stone dust, sweating and wet conditions. Injury often occurs from falls of stone or coal or from working in awkward places ; coal tattooing is the occupational mark of the collier and is seen in gross form when a leaking compressed air pipe blows coal dust at great force into the skin.

Getting dirty is unavoidable. Sneddon (1952) thought that repeated washing in older men predisposed to dermatitis. Folliculitis occurs from dirty clothes and poor skin hygiene ; pressure on the legs from leaning over the screens causes localized folliculitis in surface men. Minor sweat rashes are common and Dowling and Brain (1934) reported an epidemic. Mere physical exertion on the coal face causes great sweating. The deeper a pit is the hotter it is. Less high temperatures pertain in South Wales pits than in some others. In wet pits men may work for long periods standing in water or may have to wear oil skins. Water infusion to dampen down the dust and reduce pneumoconiosis increases the exposure.

The few chemicals encountered are the oils and greases of haulage men underground, the lubrication of automatic picks and the oiling of trams on the surface ; the alkali exposure of stone dusting with powdered limestone (to keep down explosion risk) and of cement in building operations. Leaking lamp batteries can cause acid or alkali burns on the wearer. Rubber sensitization

can result from handling water or compressed air pipes, from protective knee pads and from contact of the lamp cable with the side of the neck. Creosoted pit props and resins used for the flotation of small coal are other hazards.

Most of the occupational diseases reported in miners are infections, e.g. epidemics of boils (Edmonds, Fernandez and Bates, 1954) inflammatory cellulitis—beet hand or knee—recently shown by Atkins and Marks (1952) to follow penetration of staphylococcal hair-follicle infection to the subcutaneous tissues; and tinea pedis is now accepted as an industrial injury if exposure in pit-head baths is proved.

DERMATITIS.

In the absence of specific chemical contact a diagnosis of occupational dermatitis is seldom without question. Most agree with Sutton and Ayres (1953) that dermatitis of the hands is seldom due to one mechanism but the result of many factors, including the individual himself and his environment. The morphology of the lesions may be difficult to interpret in terms of external factors and more important therefore in diagnosis may be the site of the areas involved, which should at the onset be those most exposed to injury.

The object of this paper is to define reasonably clear patterns of dermatitis in coal miners which seem to be localized mainly by the hazards of occupation, and to suggest explanations. To this end the clinical records of 404 coal miners of South Wales with dermatitis examined in the years 1946–1955 have been studied. Where men have worked with the disorder for long periods fully developed patterns of dermatitis are reasonably common. Thyresson and Skog (1953) have pointed out that in most industries the hands, being most exposed, are the most often involved and usually show the first signs of irritation.

The cases reviewed here have therefore been classified according to the site of onset, and no attempt has been made to decide at this stage what is occupational and what is not, except to place in a separate category some typical well-defined cases of Besnier's prurigo (atopic eczema) dysidrotic eczema of feet and hands and lichen simplex chronicus (Vidal).

TABLE I.

	Cases.	%.
Forearms	10	2.5
Hands	92	22.8
Lower legs	76	18.8
Feet and ankles	81	20.0
Abdomen, buttocks and axillae	32	7.9
Neck and shoulders	19	4.7
Thighs	14	3.5
Forehead	8	2.0
Arms and legs together	13	3.2
Injury	35	8.7
Undoubted constitutional eczema (atopic)	24	5.9
Total	404	

It will be seen that the three main sites of onset of dermatitis in this series of miners are the hands (22·8%) the lower legs (18·8%) and the feet and ankles (20%).

If the hands and forearms together (25·3%) be compared with the lower legs, feet and ankles together (38·82%) the results show a preponderance of origin on the lower limbs.

Occupational Grouping.

Taking the 3 main groups of workers as—

(i) Face workers (45–55%) : (a) Hewers and getters ; Hard heading men. (b) Packers. (c) Conveyor workers. (d) Repairers.

(ii) Main road workers (25%) : (a) Repairers. (b) Haulage. (c) Others—tradesmen, etc.

(iii) Surface workers (15–25%).

The percentage distribution according to occupation is :

TABLE II.

	All cases.	Hands.	Legs.	Feet and ankles.
Face workers . . .	44	48	42	37
Main roads . . .	46	39	46	54
Surface . . .	10	13	12	9

Some surface men had contracted their dermatitis underground, but when examined were working on the surface ; this may make the incidence in this group appear higher than is true.

The figures show that in this series dermatitis of the hands is commonest in the face workers, but dermatitis of the legs, feet and ankles is more common in main road workers.

Tinea Pedis.

More cases of tinea pedis (13%) occurred with dermatitis of the feet and ankles than in the case of legs (6%) or hands (9%).

Sites of Dermatitis.

(i) *Hands and arms.*—The onset may be on the backs of the hands, between the fingers or on the fronts or backs of the forearms. Wet boring, hard heading, and awkward working are blamed in face workers ; oil and grease by haulage men. Cement dermatitis occurred in masons.

(ii) *Legs.*—Five types of dermatitis occur on the legs :

(a) Gaiter pattern just above boot-top level. This is the most common and it is lichenified in old cases.

(b) Papular, either non-follicular or follicular with actual folliculitis and boils. Occasionally discrete lichenoid papules may resemble lichen planus. Biopsy on one such case showed a dermatitis histology.

(c) A single lichenified or exudative plaque on the lower leg corresponding to an area exposed to friction when kneeling at work.

(d) Discoid patches alone, or with discoid patches on the arms like nummular eczema.

(e) Localized hypertrophic or eczematous plaques under knee pads where coal dust collects or where the man pivots on the knee at work.

Varicose veins featured only in 4 cases of the 76, but they seemed to prolong a dermatitis which had once developed.

Some had had one or more attack of leg dermatitis which had cleared up during their working life, with long free periods between.

(iii) *Feet and ankles*.—Most common is dermatitis on the dorsum of the foot or front of the ankle with lichenification and pigmentation in old cases. Working in water is often blamed. Unilateral cases are localized by venous stasis and by definite foot position as when working with one foot in water. Bilateral varicose stasis was present in 7 of 81 cases.

Less common methods of onset are by extension from tinea pedis or hyperidrotic intertrigo between the toes, frictional blisters or dermatitis on the side of the big toe which is used as a lever when working kneeling, and infective dermatitis extending from an initial dysidrotic pompholyx caused by working in rubber boots with sweating feet.

(iv) *Thighs*.—The two main types of lesions are :

(a) A papular non-follicular eruption extending from the groins to the inner aspects and fronts of the thighs, sometimes with added folliculitis and follicular scars.

(b) Plaques where the shovel is levered against the leg. In this series 3 on the left thigh and 7 on the right thigh in 10 persons.

(v) *Neck and shoulders*.—Localized plaques may correspond with pressure from automatic boring machines.

Papular and exudative patches on the back of the shoulders suggest friction of the vest and sweating, and may be associated with lesions on the axillary folds and belt area. "Droppers" of moisture from the roof are usually blamed by workmen working in very hot seams.

(vi) *Abdomen, groins, buttocks and axillae*.—Earliest lesions are non-follicular papules on the folds of the axillae or groins exposed to friction of clothing, or on the abdomen and buttocks where the belt would rub. A favourite place is over the right buttock or small of the back where a circumscribed area corresponds to the lamp battery. Relapse of dermatitis on return to work is common on these areas.

(vii) *Forehead*.—Groups of non-follicular papules occur along the pressure

area of the cap. True hat band dermatitis from leather or rubber is usually more frankly eczematous.

(viii) *Injury*.—Where dermatitis arose at the site of injury, in one-third it followed directly on the injury and in two-thirds by sensitization from topical treatment, with penicillin, sulphonamide, flavine or chloromycetin as the most common sensitizers.

DISCUSSION.

Fairly clear patterns of dermatitis in miners seem to emerge from this series.

Following a supposed lessening of resistance by constitutional or environmental factors dermatitis may become localized most commonly on the lower legs, feet, ankles or hands and less commonly on the abdomen, buttocks, groins, thighs, axillae, forehead, neck and shoulders.

Many men continue work with dermatitis for long periods or give up when the condition becomes severe. Sometimes the dermatitis remains confined to the initial site of onset and becomes thickened and lichenified. In others the eruption gradually spreads to involve fairly typical areas. Auto-sensitization from the initial site may possibly sensitize other areas of skin which later react to continued damage.

The sites involved suggest that the two main causes of localization are (i) friction of dirty clothes and trauma and (ii) sweating ; both may be present.

Trauma.—The localization on the thighs, lower legs, feet and ankles might be explained by friction of stone or coal dust rubbed by clothing on to the skin. Trauma may account for the high incidence (about 50%) of dermatitis of the hands in face workers, and although oil from automatic punchers is usually blamed by colliers this hazard is probably exaggerated.

The dermatitis will often fit the areas on hands, forearms or thighs constantly subjected to friction when the man is working in a kneeling position or resting the forearms on the thighs to shovel coal when he gets "leg weary". Definite localized and lichenified plaques of dermatitis occur on the thighs or leg from pressure of the shovel or from kneeling at work.

The abrasive property of different kinds of coal dust varies—bituminous least, steam coal more and anthracite most abrasive, with its angular and sharp splinters. Stone dust is even more abrasive because of its silica content. The rocks adjacent to the coal measures graduate through the fireclay and clays with soft particles, slippery like talc, through shales and silts with very small silica particles, to sandstone containing sand grains and finally to the most abrasive quartzite which is almost pure sharp silica. The face worker cutting through hard headings mostly contacts the hard sandstones, whereas the collier is in contact mostly with shale but this also contains many abrasive silica particles. The differing regional certification figures of dermatitis incidence

cannot be accurately related to the geology, since the general range of rocks is much the same throughout all mines in the United Kingdom, although the actual proportions differ even in individual pits. The hard anthracite coals are only found in South Wales and this may possibly increase the incidence of dermatitis in this region. Workers in sandstone quarries, however, in contact with abrasive silica rocks do not develop the same pattern of dermatitis as coal miners. Loose sand when rubbed on the skin will not abrade, but it will readily do so when firmly adherent to paper as in sandpaper. It is possible that this may explain the difference, and that the miner's skin made soft by sweating and maceration of water is easily abraded by silica particles caught up in the fabric of clothes in the manner of sandpaper. Since the introduction of pit-head baths men do not take clothes home for washing as often as formerly; often they wear torn dust-impregnated trousers for months and dirty sweat-filled socks for long periods.

A further possibility is secondary chemical sensitization to trace elements in the stone dust. Millerite, containing both nickel and cobalt, has been found in South Wales coalfields (North and Howarth, 1928) though not in the other coalfields. Chromium has not been found in South Wales. When men are working in water it is conceivable that chemical salts dissolved out of rock might be important. One American analysis (*J. Amer. med. Ass.*, 1940) quotes calcium chloride, magnesium chloride and calcium bromide as possible irritants by causing dehydration or by decomposition to irritating hydrochloric and hydrobromic acids.

Sweating. The papular non-follicular eruptions on the helmet area, under the belt, on the abdomen, under the lamp battery on the buttocks or on the axillary folds, groins and backs of the shoulders exposed to friction of clothes suggest a sweating aetiology.

Knowles (1944) has explained that sweat evaporation in miners is influenced by ventilation, humidity, and temperature, less sweat evaporating in humid atmospheres. Pits vary in these conditions.

O'Brien (1947) explained prickly heat as developing from epidermal sweat retention, vesicles resulting from closure of the sweat duct with a keratin plug. Staphylococci were considered important in association. Shelley and Harvath (1950) thought that non-specific damage to the epidermis would produce miliaria by sweat blockage, and experimentally produced the condition with adhesive tape and epidermal chemical damage. Friction of clothes and maceration of the skin under the collier's helmet, belt, battery or clothing could theoretically thicken the epidermis around the sweat orifice, and thus cause poral closure and miliaria which would later lead to dermatitis. On the other hand, a frictional or autosensitization dermatitis might be followed by a sweat block due to the inflammation itself, which would explain the quick relapse on such areas when a man resumes his normal work.

Sweating also accounts for some dermatitis of the feet by extension of intertrigo between the toes or dysidrotic eruptions and encourages the growth of fungi and bacteria.

A minority of cases are due to oil, greases, alkali, rubber sensitivity, and to the particular hazards of other tradesmen employed.

Constitutional factors of personal resistance are also important. Dermatitis of the feet and ankles is most common in main road workers. They are usually older men than face workers and their dermatitis may be long-standing (Sneddon 1952). They may be less able to withstand the effect of trauma or to recover quickly from it.

The high incidence of hand dermatitis in colliers might be explained by the greater exposure to injury of the skin at the coal face, but other factors which might lower resistance are illness, convalescence after accidents, fatigue from walking long distances to the coal face, and working at high pressure or in awkward narrow seams. Middle-aged colliers may find it difficult to keep up the sustained physical exertion required by modern methods on the coal face: some grow old more quickly than their fellows. Heron and Braithwaite (1953) found a greater degree of emotional instability in underground workers, especially in face workers, when compared with those working on the surface. This greater emotional instability of the face worker, performing a very dangerous job, in comparison with his fellow on the surface, may also perhaps make him less able to withstand emotional stresses from working conditions, home worries or bereavements and make his skin more sensitive. How much the changed conditions of the collier—reduced in status from the complete craftsman with a pride in his work to a labourer who merely shovels the coal mechanically cut for him—affect his morale, his attitude to work, his absenteeism, and his general health and skin are matters of interesting speculation.

As the hazards of coal mining seem largely physical it should be possible to reduce the risk by improved design of working clothes, boots and equipment: by proper attention to skin hygiene and working clothes, especially clean socks and trousers without holes: and by regular skin inspection to detect and treat early dermatitis. Barrier creams on frictional areas may have an advantage. Adequate skin convalescence before returning to work causing excessive sweating, and alteration of the method of wearing the belt and lamp battery might reduce the relapse rate in those cases where sweat obstruction seems to be a factor.

SUMMARY.

(1) Investigation of 404 coal miners in South Wales shows definite patterns of dermatitis and sites of onset.

(2) The commonest sites of onset are the hands, lower legs, feet and ankles and on areas corresponding to lamp battery, belt, axillary clothes contact and helmet.

(3) Trauma, sweating and positional working causing friction of dirty clothes on the skin seem mostly responsible.

(4) The rôle of sweating and water in macerating the skin and the abrasive effect of coal and stone dust with the background constitutional resistance and morale are discussed.

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SOME ASPECTS OF THE PHYSIOLOGICAL EFFECTS OF CORTISONE IN THE TREATMENT OF PEMPHIGUS VULGARIS.

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WHEN treatment of the case discussed was started about two years ago it was thought that the effects of ACTH were the same as those of cortisone, if only the equivalent dosage could be estimated; that one could change from cortisone to ACTH without risking a relapse; that salt retention with its pathological consequences was to be expected with cortisone, and therefore that a salt-poor diet must be given; and that the 17-ketosteroid excretion was necessarily some measure of adrenal function.

Mrs. R—'s case shows that all these views may be wrong in an individual case, and this analysis is published as the matter is of great importance in the day-to-day handling of hormone therapy.

In describing the case only those details which illustrate the points discussed are brought forward, as it is thought that unnecessary details would merely obscure the issue.

CASE REPORT.

Mrs. R—, aged 54 years, is suffering from pemphigus vulgaris of two and a half years' duration, and has been treated with cortisone or ACTH for more than two years.

The diagnosis has been confirmed by the intra-epithelial site of the bullae, and by the demonstration of acantholytic cells in scrapings from the floor of the lesions by Tzanck's method.

She is at present free from lesions and complications, except for some deposit of fat over the shoulders, upper part of the back, and breasts.

She has a maintenance dose of $37\frac{1}{2}$ mg. of cortisone a day, with periodic courses of methylandrostendiol, and potassium citrate.

First Course of Hormone Therapy.

She was given a course of ACTH (Fig. 1), 100 units for 13 days, 75 for one week, 50 for one day, and finally 25 for 3 days.

There was a partial remission of her skin condition during the course of treatment but severe crops of large bullae appeared around the eyes, which became infected with an organism resistant to the usual antibiotics, and this was cleared with difficulty.

Owing to shortage of supplies treatment was suspended on the twenty-fifth day, and she relapsed at once.

Prior to treatment her 17-ketosteroid excretion was 3 mg. per 24 hours (normal 5–15); after 9 days, stimulation with 100 units of ACTH this rose to 15, but it fell to 9 on reduction of the dose: this should be compared with the rise to 58 obtained with the same dosage in 13 days in a case of erythrodermia.

The eosinophil count was 119 per c.mm. before treatment, fell to 94 after 7 days, and to 6 after a further week.

The incomplete response of the skin, the low initial level of the ketosteroids, the small rise obtained after ACTH in relatively large dosage, and the absence of any significant fall in the eosinophil count for the first week, show that the adrenal cortex was in a state of depression, and it should be noted that the patient had had no cortisone at that date.

Treatment with Cortisone.

When supplies became available she was given cortisone, and was soon stabilised on 150 mg., completely free from lesions.

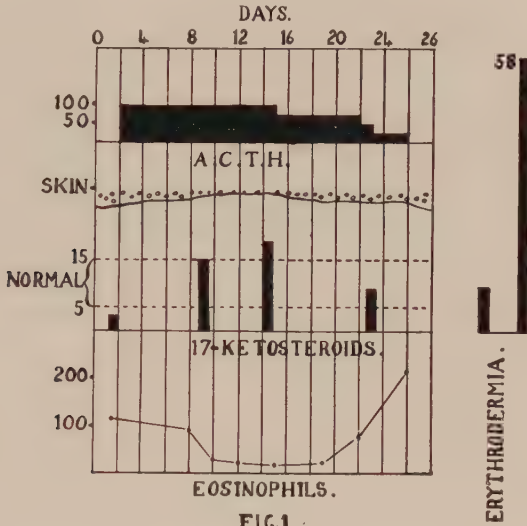


FIG. 1.—ACTH in units, 17-ketosteroids in mg./24 hours, and eosinophils per c.mm

Second Course of ACTH.

While she was stabilised on 150 mg. of cortisone, it was feared that considerable adrenal depression might result from the action of that hormone, and it was decided to give a "boosting" course of ACTH: Accordingly, 80 units of ACTH gel were given instead of the cortisone, but after one day this was suspended owing to local reactions: there was an immediate relapse, and treatment was resumed after 24 hours with 100 mg. of cortisone and 40 units of water-soluble ACTH. The cortisone was stopped on the fourth day, and 100 units ACTH was then given alone. The skin condition cleared, and cortisone, 150 mg., was resumed on the fifteenth day.

This episode illustrates two possible hazards which may be encountered on changing from cortisone to ACTH: first, intolerance to the particular type or batch of ACTH (another patient developed a widespread erythematous-urticarial eruption on water-soluble ACTH which subsided rapidly on changing to another batch); and second, clinical relapse.

And it also illustrates, when compared with subsequent episodes, the advantage of using a cortisone "umbrella" during such a switch over.

Third Course of ACTH.

This course was given because of the orthodox opinion that adrenal depression should be countered by periodic courses of ACTH.

At the time the patient was stabilized on 100 mg. of cortisone, and when 120 units of ACTH was substituted there was an immediate relapse, which was controlled only after changing back to cortisone eleven days later at a dosage of 250 mg. daily (Fig. 2).

The 17-ketosteroid figures are instructive. Prior to the change they were just above normal; on the fourth day of ACTH they fell to 3, and even after 10 days' stimulation the figure only rose to 7, while after the change back to cortisone it rose to 18. The explanation must be that the high level before and after ACTH was due to excretion of hydroxycorticoids along that channel.

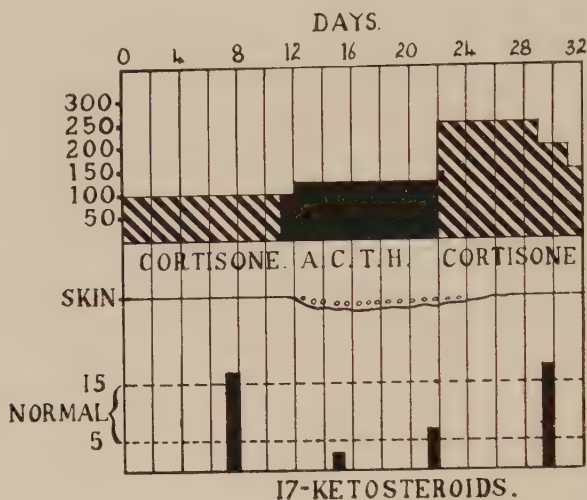


FIG. 2.

FIG. 2.—ACTH in units, cortisone in mg., 17-ketosteroids in mg./24 hours.

This episode illustrates again the clinical relapse on changing from cortisone to ACTH, the much greater dose of cortisone required to regain control than was necessary as a maintenance dose beforehand, and finally the disappointing adrenal response, as indicated by the 17-ketosteroid excretion after 10 days' stimulation with relatively high doses of ACTH.

Fourth Course of ACTH.

A fourth course of ACTH was given at a time when the maintenance dose of cortisone was 50 mg. The result was again an immediate relapse, which was controlled only after cortisone had been resumed, and the dosage raised to 200 mg (Fig. 3).

On this occasion 100 units of ACTH was given for 6 days and 180 units for 12 days, and in spite of this very great stimulation the 17-ketosteroid excretion only rose to 8.

Summary of Cortisone Therapy in this Case.

Cortisone rapidly controlled the disease, the first time it was used and also after every relapse; the progress of the patient was most satisfactory, with minimal disturbances. This may be contrasted with the stormy incidents when treatment with ACTH was given.

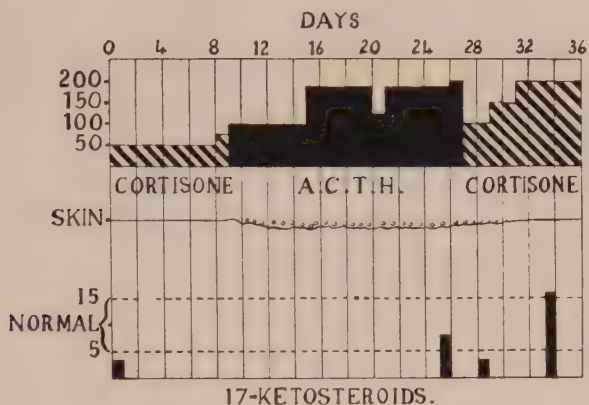


FIG. 3.

FIG. 3.—ACTH in units, cortisone in mg., and 17-ketosteroids in mg./24 hours.

DISCUSSION.

Equivalent Dose of ACTH and Cortisone.

Sulzberger suggested at the Tenth International Congress of Dermatology in 1952 that a rough guide to the equivalent dosage of these hormones was that one unit of ACTH intramuscularly could be taken as being equal to $2\frac{1}{2}$ to 4 mg. of cortisone orally.

In the present case, if the fourth course of ACTH is considered, it will be seen that she was free from lesions on 50 mg. of cortisone, and it might therefore be expected that 20 units of ACTH would have been an ample dose to retain control of the remission; actually, however, 100 units was insufficient and even raising the amount to 180 units failed to induce a remission.

Ogryzlo and Gormall (1953) found large variations in potency in different samples of commercial ACTH, and these variations were sufficient to make the estimation of dosage equivalent to an effective dose of cortisone largely a matter of guesswork, even in cases where the adrenals were fully functional.

The effects of ACTH depend on the strength of the sample and on the state of the adrenals, and cannot therefore be correlated with an effective dose of cortisone with any accuracy.

Functional Adrenal Depression during Cortisone Therapy.

It is well known that there is adrenal depression during cortisone therapy, but it is much more severe than is generally recognized.

Ingle and Baker (1953) state that overdosage with cortisone induces involution of the zona fasciculata of the adrenal cortex in man, by suppressing the

endogenous secretion of ACTH. Salassa *et al.* (1953) of the Mayo Clinic have stressed the importance of this depression, and have instanced two deaths after operation, in patients who had been on cortisone therapy, due to the failure of the depressed adrenals to respond to the stress of the surgical procedures. They are of the opinion that all patients who have been treated with cortisone within the previous three to six months should be viewed with great care, and given cortisone both pre- and post-operatively.

Fraser *et al.* (1952) reported a case of sudden death after an operation on the hip in a patient who had been treated with cortisone for eight months, and who had been deprived of the hormone two days before the operation; severe adrenal atrophy was found at autopsy.

Gordan (1952), in an editorial comment on Fraser's case, expresses his opinion that adrenal atrophy is to be expected in patients who have been taking cortisone for long periods, and points out that this hormone is actually given to depress adrenal function in cases of female pseudohermaphroditism and macrogenitosomia.

In the present case it will be seen that there was a steady decrease in the response to ACTH as the period of cortisone therapy grew longer.

Other Causes of Failure of the Adrenals to Respond to ACTH.

As the action of ACTH is to stimulate the adrenal cortex to produce its hormones, it is evident that any disease process that damages the cortex may interfere with the action of ACTH to a greater or less extent.

Caccialanza and his co-workers (1953) examined the adrenocortical function in eight cases of pemphigus vulgaris and found no significant increase in 17-ketosteroid excretion after the injection of a small dose of ACTH, in contrast to the comparatively large increases they obtained in cases of dermatitis herpetiformis. They concluded that there was adrenal insufficiency in pemphigus vulgaris, and doubted whether the use of ACTH in that disease is justified, since constant stimulation of a damaged organ may lead to complete functional exhaustion.

Quiroga and Corti (1954) found 17-ketosteroid levels of from 2.02 to 3.45 mg. daily in eight cases of pemphigus vulgaris, and similar figures in four out of five cases of pemphigus foliaceus; they even suggest that this low figure could be used in the differential diagnosis of these conditions from other bullous eruptions.

Goldzieher (1945) found adrenal atrophy in six cases of pemphigus vulgaris at autopsy. He described acute degenerative and inflammatory changes, necrobiosis, loss of cells, depletion of lipid, nodular hyperplasia and fibrosis, and he considered that these findings suggested continual damage, leading to scarring and attempts at repair. The degree of damage seemed to bear some

relationship to the duration of the disease, and he believed that there must have been some degree of adrenal insufficiency during life.

Since adrenal insufficiency has been found in these twenty-two cases by three different observers, it must be expected that ACTH will be ineffective in at least some cases of this disease.

Hill *et al.* (1950) found that there was some evidence of a delayed or inadequate response to ACTH in hypothyroidism.

Estimation of Adrenal Function.

Consideration of the present case, and the findings cited above regarding depression of adrenal function, both by the disease itself and by cortisone treatment, make it necessary to estimate the adrenal reserve before giving ACTH. The adrenal response required for successful treatment is greatly in excess of the normal physiological requirements of the body, and a gland which is quite able to respond to the day-to-day requirements of the body, or even to minor emergencies, may nevertheless be quite unable to supply the very large amounts of steroids necessary for the control of a disease such as pemphigus.

The standard tests for adrenal function are the 48-hour ACTH test with the determination of the 17-ketosteroids, and even more important the 17-hydroxycorticoids, and the 8-hour intravenous ACTH test. In patients who have had no cortisone these tests should indicate patients whose adrenals are unlikely to respond sufficiently, but in those who are already being treated with cortisone they cannot be done without stopping the treatment. In the present case a high 17-ketosteroid output during cortisone treatment was compatible with an extremely poor response to ACTH. A further difficulty is that these tests may take many days, and a clinical decision may have to be made before the results are available. The dermatologist has an advantage over clinicians in other branches of medicine in that he is able to assess response by observing the skin lesions, a shower of fresh bullae being a concrete fact.

Has ACTH the Same Action as Cortisone in Pharmacological Dosage?

Sampson Wright (1952) states that the only action of ACTH is to stimulate the adrenal cortex, and it must be remembered that of about 29 steroid hormones isolated from the adrenal cortex, only six have been found to have a cortisone-like effect; others have actions upon electrolyte metabolism, which cortisone influences only slightly (Ingle and Baker, 1953).

In normal circumstances the secretion of ACTH by the pituitary results in a balanced output of these steroids; but large amounts of cortisone are required for the control of diseases such as pemphigus, and it is reasonable to suppose that excessive quantities of other steroids will be released at

the same time under the stimulus of ACTH, and that undesirable side-effects due to them are thus likely to develop. With cortisone, on the other hand, only the quantity required for the control of the disease will be given; the production of endogenous ACTH will be suppressed, and as the adrenal gland itself will be in a state of depression, those other steroids will be formed to only a limited extent, and any disturbance in the salt and water balance will be due to the much weaker action of cortisone itself, which Goldsmith and Hellier (1954) state to be only one-thirtieth of that due to the desoxycorticoids. As the tendency of cortisone is to increase katabolism, and that of the androgens to oppose this, one would expect that there would be a greater breakdown of protein when cortisone is employed than when ACTH is used.

Minimizing the Toxic Effects of Cortisone.

Winter *et al.* (1953) found that testosterone propionate and methylandrostendiol tended to prevent the adrenal atrophy produced by cortisone in rats without interfering with its anti-inflammatory action, and that if both cortisone and methylandrostendiol were given together there was recovery from the damage already done by cortisone itself.

In the present case there has been some indication of an improvement in adrenal function following the administration of 10 mg. of methylandrostendiol daily for eight months, while on 50 mg. of cortisone daily, in that her 17-ketosteroid excretion rose from the Addisonian level of 1.2 mg. a day to 7.3.

As the dosage of cortisone remained the same at 50 mg., it is not probable that this rise in output could be due to simply excretion of hydroxycorticoids along this channel, especially since the improvement was maintained after the methylandrostendiol was stopped. A similar finding occurred in a patient with dermatitis herpetiformis, the output rising from 0.8 to 5.2 mg.

One result of protein breakdown is the development of osteoporosis, due to a defect in the protein matrix of bone. In this case of dermatitis herpetiformis skiagrams revealed osteoporosis of one of the dorsal vertebrae, which may have been senile in origin as the patient was over 70 years of age; this has been kept in check by methylandrostendiol, according to three-monthly routine x-ray examinations. She sustained a fracture of her wrist, and there was no bony union until the dosage of methylandrostendiol was raised to 100 mg. daily, after which satisfactory but slow progress was made.

Potassium deficiency can be an important complication, both of ACTH and cortisone therapy, and may be very insidious in its development.

In the present case muscular weakness and a feeling of tiredness was accompanied by a low serum or red-cell potassium level, and these symptoms

disappeared when 30 grains of potassium citrate was given four times a day. In another case during cortisone treatment a low serum potassium was found to coincide with cerebral excitement, and was relieved by an appropriate potassium intake.

Cort and Matthews (1954) found large deficits of potassium in three cases of congestive heart failure, and in one of these large doses of potassium cleared the oedema, including the salt retention. In another patient treated with cortisone observed by the writer, there were mild symptoms of cardiac failure, with oedema of the ankles and breathlessness on exertion, which was rapidly cleared by large doses of potassium citrate; the biochemical findings were a low serum potassium and a low normal serum sodium.

High serum sodium levels and clinical oedema have not been a feature in the cases observed by me. In the case reported here, the levels have been in the neighbourhood of low normal, and on occasions there has been an actual base deficiency. Although it is possible to get salt retention with low serum sodium figures, it seems that drastic salt restriction should not be enforced during cortisone treatment in the absence of biochemical or clinical grounds.

With ACTH, on the other hand, the excessive production of desoxycorticoids is much more likely to produce a state in which salt retention occurs. In the management of cases on cortisone it is therefore important to pay special attention to the red-cell potassium, and to the serum potassium levels.

ACTH or Cortisone?

Pemphigus vulgaris is a disease in which a fatal outcome is to be expected, and the only treatment that holds out any reasonable hope of success is the use of these hormones. The period of treatment, as far as our present knowledge goes, is likely to be for life.

Both hormones have advantages and disadvantages. An outstanding feature of cortisone therapy is the depression of adrenal function, and since treatment must be long continued, the hormone will have to be given to outpatients; there is then the risk of the patient omitting to take his tablets, with the consequent possibility of death from adrenal failure. On the other hand, it is often said that ACTH leads to adrenal hypertrophy, and therefore this risk does not arise. But it must be remembered that the endogenous secretion of ACTH is depressed by giving that hormone, and its sudden stoppage may well result in secondary adrenal failure. The main disadvantage of ACTH is that it depends for its action on the integrity of the adrenal cortex, and as it has been shown above, there is almost certain to be damage to that tissue by the disease process so that the effects of the hormone cannot be forecast accurately.

The use of cortisone and periodical "boosting" courses of ACTH under an umbrella of cortisone to revive the adrenals has been advocated by Bonner and Homberger (1952), but, as has been discussed above, the depression of the adrenals is considerable and they cannot resume function until a good deal of time has elapsed. If there is a sudden change from cortisone to ACTH a relapse in the disease is to be expected, and large doses of cortisone may have to be given in order to regain control. This was well shown in the present case.

In this connection the observations of Liddle *et al.* that there is a steady increase in the urinary 17-hydroxycorticoids when a standard daily dose of ACTH is given for twelve days, show that even in the normal subject time is required for ACTH to have its full effect.

The great advantage of cortisone is that the exact dose required can be given, and that the side effects, other than those due to cortisone itself, are caused by the lack of other hormones or electrolytes which can be corrected by replacement therapy; this is in contrast to the overproduction of desoxycorticoids which may be expected with ACTH.

After weighing the evidence, and drawing on his own experience, the writer inclines to the view that it is better to "write off" the adrenals in this disease, and to rely on substitution therapy to counteract the side effects. It must be remembered that the same amount of cortisone that is necessary to control the disease is required, whether it is produced from the patient's own adrenals under the stimulation of ACTH or is given in tablet form, so that the hormonal effects of cortisone are likely to be present in either case.

SUMMARY.

The response of a case of pemphigus vulgaris to treatment with cortisone over a period of two years is analysed, and commented upon from a practical point of view.

Evidence is brought forward to show that there is likely to be adrenocortical damage in this disease, and that therefore ACTH is unreliable as a therapeutic agent.

The adrenal depression due to cortisone is discussed, and is shown to be much greater than is generally realized. A sudden change from cortisone to ACTH is likely to be followed by a relapse of the disease, or in long-term cases even by adrenal failure. Thus a "boosting" course of ACTH to maintain the integrity of the adrenal cortex is a risky procedure.

The actions of ACTH and cortisone are discussed, and the opinion is put forward that the two hormones differ in their actions, ACTH tending to produce excessive quantities of desoxycorticoids with their powerful effects on salt and water metabolism, and cortisone tending to suppress these steroids, and also the androgens, with their opposing action to cortisone on protein metabolism.

As ACTH is unreliable, and substitution therapy is easier than dealing with excessive quantities of unwanted hormones, the opinion is advanced that cortisone, and not ACTH, is the treatment of choice in pemphigus.

Other details of steroid therapy are discussed.

I am indebted to Dr. Ian Anderson for the biochemical investigations and their interpretations, and to Dr. M. Sloan Smith for permission to publish the case.

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TROPHIC CHANGES IN THE SKIN AFTER OPERATIONS ON THE TRIGEMINAL NERVE

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TROPHIC changes in the skin are surprisingly uncommon after operations for the relief of trigeminal neuralgia. In the few cases which have been reported in the literature a curious punched-out ulceration of the ala nasi has usually occurred, which may at first sight suggest a neoplastic or a specific inflammatory process.

Three further case histories are given.

CASE REPORTS.

CASE 1.—A woman aged 41 was first seen in 1951. Left-sided trigeminal neuralgia had begun in 1942, and alcohol injection of the Gasserian ganglion was done in March 1948, producing complete anaesthesia in all divisions of the nerve.

Within two months there was crusting in the left nostril and two or three superficial ulcers on the left cheek.

In December 1948 alcohol injection of the left Gasserian ganglion was repeated because pain had recurred in the area of the third division of the trigeminal nerve. Cervical sympathectomy was also done as treatment for the ulcers.

In 1951 there was further recurrence of pain in the same area of the left trigeminal nerve.

The left side of the nose was ulcerated. The alar cartilage was destroyed, giving a very marked punched-out effect. There was crusting in the left nasal vestibule and scarring on the upper lip adjacent to the ulcerated area (Fig. 1). Sensation was diminished in the areas of the first and second divisions of the left fifth nerve. The left corneal reflex was absent and there was a left-sided Horner's syndrome.

Section of the root of the left fifth nerve relieved her pain, but the skin lesions persisted, and the patient became very depressed about the deformity of her nose. A plastic repair was attempted but ulceration of the nose recurred after grafts had taken satisfactorily.

She was admitted to the Psychiatric Unit because it was thought that the skin lesions might be to a certain extent self inflicted. A diagnosis was made of anxiety hysteria in a feeble minded person.

CASE 2.—A woman aged 77 attended hospital in September 1954 because of soreness and recurrent bleeding from the left nostril for one year. In 1950 the left Gasserian ganglion had been injected with alcohol to relieve neuralgia.

On examination there was ulceration of the left nostril, with a punched-out defect in the posterior part of the alar margin, and crusting in the nasal vestibule. There was slight scarring on the upper lip adjacent to the ulceration (Fig. 2). Sensation was diminished in all divisions of the left fifth nerve.

Biopsy of the lesion of the nose showed chronic non-specific inflammatory changes.

When questioned she said that there was often irritation of the side of the nose and that the left side of the face felt bigger than the right side.

CASE 3.—A woman aged 65 attended hospital in July 1954. Ten years previously the lower two-thirds of the sensory root of the left trigeminal nerve had been cut to relieve neuralgia. As far as she could remember, soreness of the left nostril had begun within three months of the operation, and it had persisted. There had been gradual loss of tissue and recurrent bleeding from the left nostril.

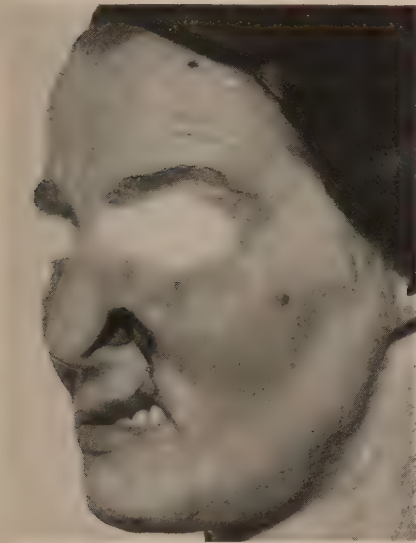


FIG. 1.



FIG. 2.

On examination there was crusting and slight loss of tissue of the left ala nasi. The tissue loss was sharply defined and similar to that in the previous cases, as if a bite had been taken from the posterior edge of the nostril. The crusts could be removed easily, leaving a moist surface which oozed blood.

The patient denied that she picked the lesion, but said that she constantly dabbed it with her handkerchief because of bleeding.

DISCUSSION.

Trophic changes in the skin following section of the sensory root or alcohol injection of the ganglion of the trigeminal nerve are very uncommon. Adson (1926) reported the results of 587 cases of trigeminal neuralgia treated by operation at the Mayo Clinic, without mentioning this complication. Harris (1940), in a series of 1433 cases of trigeminal neuralgia treated by alcohol injection, stated that trophic lesions may occur very occasionally. However, McKenzie (1933) found two cases of ulceration of the nose among 78 patients who answered a questionnaire on the effects of their operation, and mentioned a third case which followed section of the fifth nerve during surgical removal of an acoustic

neuroma. Similar cases have been reported by Loveman (1933), Jaeger (1950) 3 cases, Tappeiner (1951), Hodgson (1952) and Stuhmer (1952). All the reported cases, except that of Tappeiner, have been in women. Harris found twice as many women as men suffering from trigeminal neuralgia.

The skin lesions usually begin within a few months of operation. However, in Stuhmer's patient the interval was $3\frac{1}{2}$ years and in Case 2 it was 3 years. All these cases showed a characteristic ulceration of the ala nasi, the most striking feature of which is the "punched-out", "crescentic" or "bitten-out" appearance of the defect in the cartilage. Crusting in the nasal vestibule occurs and the crusts can easily be removed, showing a moist red surface which tends to bleed. There may be some scarring on the upper lip adjacent to the ulceration. The appearance of the ulcer is so constant that when the history of operation on the trigeminal nerve is obtained it can usually be distinguished with confidence from ulceration due to neoplastic or chronic specific inflammatory processes.

Other skin lesions were sometimes found, as in Case 1. Stuhmer's case showed superficial crusted ulcers on the cheek, depigmented areas and a wedge-shaped patch of alopecia, with the characteristics of alopecia areata, in the temporal region. In Loveman's case there were ulcers on the forehead and a patch of alopecia which appears to have been secondary to ulcers in the scalp. Becker (1925) and Netherton (1933) each described eczematoid dermatitis occurring on the face after section of the sensory root of the fifth nerve, which they regarded as a trophic change.

Trophic lesions of the skin may also follow disease of the trigeminal nerve or its connections in the central nervous system. Rosenberg and Solovay (1939) reported two cases of ulceration of the nose in patients with post-encephalitic Parkinsonism. Rook (1952) described the characteristic crescent defect of the ala nasi in a patient with partial anaesthesia of the left fifth nerve, bilateral ptosis and unequal pupils. Karnosh and Scherb (1940) found ulcers on one side of the face in a patient with thrombosis of the inferior cerebellar artery, and in a patient with syringobulbia. Darier (1937) reported trophic ulcers of the nose and palate in a tabetic.

Because of the consistent pattern of the skin lesions there seems little doubt that they are trophic changes secondary to interruption of the sensory pathway of the fifth nerve. Tappeiner thought that trophic ulceration did not occur if the sensory root of the fifth nerve was cut completely. However, Loveman's case, in which complete section of the sensory root was done, must disprove this. Harris (1954) states that he has never seen trophic ulceration follow sectioning of the branches distal to the Gasserian ganglion.

There remains the question of whether there is any contributory factor apart from trophic disturbance which accounts for ulceration occurring in only a few cases. It is possible that many of the patients in whom ulceration occurs

are liable to pick and scratch their skin unduly. After operation on the fifth nerve there may be paraesthesiae and a sensation that the nostril on the anaesthetic side is blocked, which may result in constant picking. Certainly in Case 1 the personality of the patient was such that dermatitis artefacta was considered. In Case 2 the patient said that there was often irritation of the side of the nose, and she was conscious of the anaesthetic side of the face feeling abnormally large. Loveman suggested the possibility of dermatitis artefacta in his case, and in Stuhmer's case the patient suffered from widespread neuro-dermatitis of the face and scalp in areas which were not anaesthetic.

Treatment in general is unsatisfactory. McKenzie reported that in two of his three patients healing occurred after cervical sympathectomy. Harris also advised this treatment. However, cervical sympathectomy did not have any effect in Case 1. Loveman treated his case by radiotherapy, but the slow healing which resulted may have been due to local hygiene and the application of ammoniated mercury ointment. In most cases it seems that local measures directed against secondary infection and avoidance of trauma will produce as good results as more radical methods of treatment.

SUMMARY.

Three cases are described in which trophic ulceration of the skin occurred after operation on the trigeminal nerve for neuralgia. Attention is drawn to the characteristic crescentic ulceration of the ala nasi which has occurred in many recorded cases. The literature is reviewed and discussed.

I wish to thank Dr. G. B. Dowling, Dr. G. B. Mitchell-Heggs, and Dr. A. J. Rook for permission to describe their patients, and also for their help and encouragement. I am indebted to the Photographic Departments of the Medical Schools at St. Thomas's Hospital and at St. Mary's Hospital for the illustrations of Case 1 and Case 2 respectively.

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ERYTHEMA ELEVATUM DIUTINUM.

A NOTE ON THE HISTOLOGY OF THE ORIGINAL CASE.

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IN 1894, Radcliffe-Crocker and Campbell Williams described a case under the title "erythema elevatum diutinum". They also compared their case with others seen by Bury and Hutchinson. Those who have subsequently made this diagnosis have had difficulty in identifying their cases with the original. Radcliffe-Crocker's (1903) description of the latter is called "*assez vague*" in Darier's *Précis* (1947): It should be pointed out that the original clinical description was highly detailed; any vagueness arises from the authors' caution in defining the diagnostic boundaries. They stated "it may be safely assumed that the number of cases is too small to afford us a complete symptomatology of these forms of disease".

Their account of the histological findings in their case is more open to criticism. It has been called "vague in respect to cytologic detail" (Weidman and Besancon, 1929), "too brief to make identification certain" (Ketron, 1944) and quite frankly "very poor and not diagnostic" (Haber, 1955). It is in fact expressed in very general terms and the sense of the text is not materially amplified by the two sketches which accompany it. They described a fibrocellular mass extending between the epidermis and the level of the coil glands, in great part replacing the normal fibres of the corium. The unidentified "cells" were either distributed between the new fibres, which followed the course of the blood vessels, or were grouped into clumps where they predominated over the fibrous elements. Hair follicles and sebaceous glands were absent, but sweat glands remained. The blood vessels were normal apart from slight thickening of the outer wall, and there was no marked dilatation of the lumen.

On grounds of the inadequacy of the original description Ketron (1944) suggested that it should be abandoned for purposes of identification and that the cases reported by Weidman and Besancon (1929) should be accepted as typical particularly with regard to the histology. This left the original case as a disembodied phantom, a name without a disease, the smile without the cat. In an effort to lay this elusive ghost, I attempted to find out more about little Amy Holland, who in 1893, at the age of six, was anaesthetised with chloroform to yield the biopsy in dispute.

Unfortunately, no trace of the original case records could be found at University College Hospital, from which they are thought to have departed in

a paper salvage drive during the Great War. Inquiry at the Victoria Hospital for Children, where the case was first seen, was equally fruitless. The records of that hospital were also war casualties having been destroyed in an air raid in 1941. Collections of Radcliffe-Crocker's papers housed at University College Hospital Medical School and the Royal Society of Medicine added no fresh information. The remaining hope rested in an uncatalogued collection of histological sections belonging to Radcliffe-Crocker. These had been kept in the Dermatological Department for historical interest. Many of the earlier sections dating back to the 1870's are thick little chips of tissue, deeply stained with logwood and carmine, and are histologically unrecognizable. The later sections, many of which were cut by Pernet, are more elegant. They are relatively thick and the stains have faded, but they are otherwise well preserved. Sir Archibald Gray suggested to me some years ago that it might be interesting to try to restrain some of them. This advice went unheeded until, during a recent search of this collection, five slides came to light, each labelled "erythema elevatum diutinum". The slides were numbered serially 1-5, dated 22 January 1894, and bore the name Holland and the words "knuckle" or "hand". Slide No. 1 carried a small label reading "drawn low" and an ink mark on the coverslip near one of the sections. Slide No. 3 was inscribed "drawn high" and traces of an ink mark could be discerned on its cover-glass (Fig. 1). The diagnosis, date, name and site strongly suggested that these sections came from the original case. It remained to examine the section on slide No. 1 indicated as having been drawn under the low power of the microscope. This showed a low-power field closely resembling Fig. 1 in the original paper (Fig. 2, *a* and *b*).

The cover-glasses were removed by soaking in xylol overnight. The sections were floated off into alcohol and taken through to water. They were then decolorised with dilute hydrochloric acid and restained individually. With haematoxylin and eosin, van Gieson's stain, acid orcein and methylene blue, Mallory's triple stain, toluidine blue and a ferrocyanide technique for iron, the results were technically satisfactory. Staining by the Unna-Pappenheim and Giemsa methods yielded poor results, possibly due to the original fixation in a mixture of alcohol and 1/6% chromic acid.

Thirteen separate pieces of tissue are available. It seems probable that they are all from the same biopsy, only one of which is mentioned by Radcliffe-Crocker and Williams. Those slides originally labelled "knuckle" bear sections differing from those on one labelled "hand" only in the presence of hypodermal tissue in the former. It is possible that the biopsy was wedge-shaped in the transverse plane and that the sections which extend into the hypoderm came from the middle of the block.

Microscopical examination reveals that the epidermis is substantially normal, but hair follicles and sebaceous glands are absent. Sweat ducts and coils

remain. The lesion consists of a mass of young fibrous tissue extending from the papillary body to the upper margin of the hypodermal fat (Fig. 3). The superficial blood vessels are a little dilated and there appears to be a slight condensation of fibres around them. No "toxic hyaline" is detectable. A

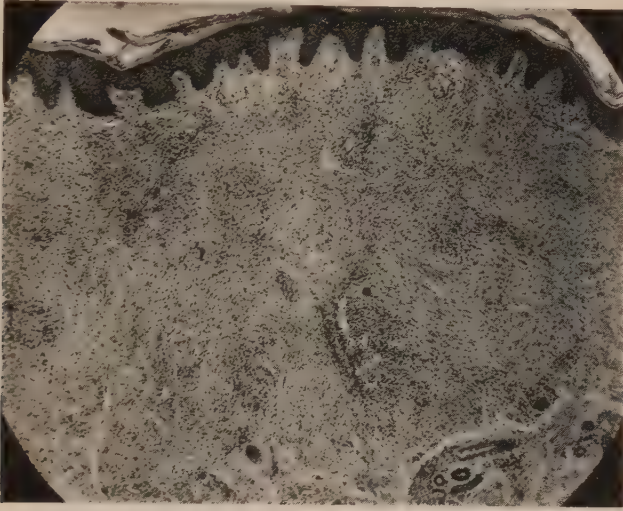


FIG. 3.—H. & E. / 55.

cellular infiltrate is present, partly perivascular and otherwise diffuse. It is composed of lymphocytes, histiocytes and polymorphonuclear neutrophils (Fig. 4), with a smaller number of eosinophils and plasma cells, scanty mast cells and a very small number of giant cells (Fig. 5). The latter are seen near a small pale-staining amorphous area high in the dermis, possibly an old

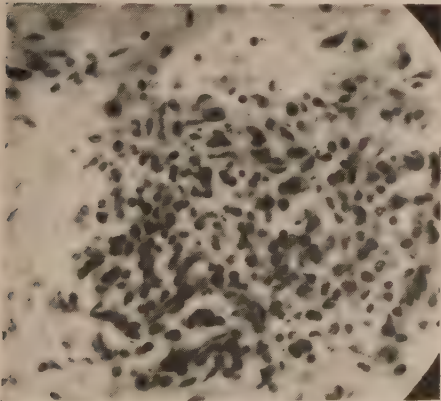


FIG. 4.—H. & E. $\times 450$.

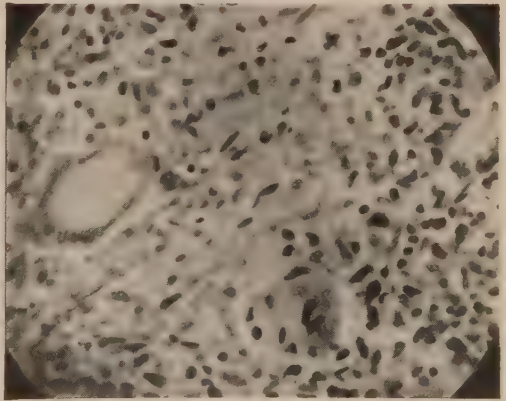


FIG. 5.—Toluidine blue. $\times 450$.

necrosis. This area and the nature and arrangement of the neighbouring infiltrate are unlike the appearances in granuloma annulare. Neither tissue metachromasia nor iron is present, elastic tissue (Fig. 6) is almost completely absent in the lesion and no doubly refractile particles are seen with polarised light.

The appearances are those described in more general terms by Radcliffe-Crocker and Williams. They are not those of granuloma annulare or of the

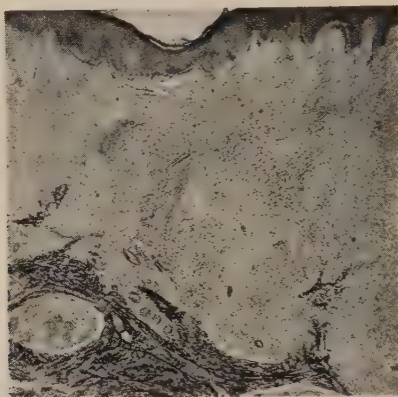


FIG. 6.—Acid orcein and methylene blue. $\times 55$.

subcutaneous nodules of rheumatism, but resemble the changes ascribed to erythema elevatum diutinum by Weidman and Besancon (1929) and others. No "toxic hyaline" was detected, but according to Ketron (1944) this change occurs at a penultimate stage in the development of the disease; it was absent in Haber's case (1955). A few giant cells were seen, but this may be an incidental rather than an essential feature.

SUMMARY.

Sections believed to be those of the original case of erythema elevatum diutinum have been discovered and restained. They show the general changes attributed to this disease by later observers, viz. acute inflammation evidenced by polymorphonuclear leucocytes, combined with fibrosis of the corium.

I am indebted to Mrs. J. Hardy for her skilful restoration of the sections. Fig. 2, *a*, is reproduced from the *British Journal of Dermatology*, 6, 1894.

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THERAPEUTIC DYES : A NEW METHOD OF OVERCOMING THEIR DISFIGURING PROPERTIES.

DR. HERMANN EPHRAIM

Haifa, Israel.

CERTAIN chemical dyes are, as is well known, very efficient therapeutic agents. The therapeutic dyes mainly used originate from Acridine dyes (flavins) and Rosaniline dyes (triphenylmethane); from the latter group those most commonly used are gentian and methyl violet, brilliant green and basic fuchsin. The dyestuffs are divided into two groups according to their reaction, whether basic or acid, the former having a special affinity for Gram positive, the latter for Gram negative, organisms. Besides their bacteriostatic action the dyes are therapeutically important as fungicides.

Another therapeutic field is the use of gentian violet in the treatment of certain eczemas. Bacterial processes on the skin are much more frequently an aetiological factor in eczema than is generally supposed, and the favourable influence of the dyes in numerous cases of eczema is certainly to be attributed to their bactericidal property. The bactericidal anti-inflammatory and epithelizing activities of gentian violet explain its very favourable influence on obstinate ulcerations.

The healing action of the dyes in the treatment of burns is mainly due to their valuable property of penetrating dead tissue and thus counteracting the danger of infection. Another important but relatively seldom utilised property of gentian violet is its antipruriginous action.

The therapeutic value of a medicament must be defined not solely by its efficiency against bacteria or its influence on certain states of disease but also by its influence on normal tissues. The absence of irritating or sensitizing tendencies in the commonly used dyes gives them a most important advantage over other common bactericides, including sulphanilamide and the antibiotics. Johnson (1948) states in his review of the common antibacterial remedies: "Nothing appears to be acceptable for any period of time", and regarding the chemical dyes only: "Their application is inconvenient for the patient". Pillsbury (1946) writes "Unfortunately a non-sensitizing and completely satisfactory method of treatment is not yet available: gentian violet is widely used but messy and disfiguring; acriflavine is messy but extremely effective".

2. *Aqueous Paste* :

Sulph. precip.	.	.	.	.	.	.	.	3.0
Acid. salicyl.	.	.	.	.	.	.	.	1.0
Acriflavine	.	.	.	.	.	.	.	0.014
Basic fuchsin	.	.	.	.	.	.	.	0.011
Gentian violet (I.C.I.)	.	.	.	.	.	.	.	0.001
Bentonite	.	.	.	.	.	.	.	0.2
Aqua dest.	.	.	.	.	.	.	.	1.0
Glycerine	.	.	.	.	.	.	.	2.0
Titanium dioxide	.	.	.	.	.	.	.	3.0 (Parts by weight)

Intensity or shade of colour is easily modified.

Finally, it is worth mentioning that the new method besides making possible the unrestricted use of dyes also puts at the doctor's disposal cosmetic-therapeutic (since skin-coloured) preparations for different indications which is often of great value, particularly on uncovered parts of the body.

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BOOK REVIEW

SYSTEMIC ASSOCIATIONS OF SKIN DISEASES.*

THERE will not, I trust, be confusion between this work and Dr. Kurt Wiener's previous work, *Skin Manifestations of Internal Disorder*. The present book is in fact a companion volume to the other and deals with the systemic aspects of those skin conditions which produce systemic changes, or which are due to endogenous factors. It is a remarkable example of Dr. Wiener's industry, as is shown by its 2759 references, and is a mine of information.

The first few chapters deal with those diseases which fall into the no-man's-land between general medicine and dermatology—lupus erythematosus, scleroderma and dermatomyositis and then follow the erythemas, multiforme and nodosum. Here one feels that Dr. Wiener is at his best; the clinical features are described admirably and the reproductions of the radiographs and pathological sections are excellent.

In later chapters the systemic aspects of more mundane dermatological conditions such as acne, eczema, urticaria, pruritus and psoriasis are dealt with and at times the author is straining at a gnat to discover the systemic aspect of conditions like lichen planus.

It is a pity that in the chapter on pemphigus Dr. Wiener has not mentioned recent work on the histology of blisters which has led to a better classification of this group of diseases and yet has found space for a page on the Pels-Macht test.

Treatment is discussed at the end of each chapter and the second half of the book deals with the systemic treatment of skin disease, pride of place being given to ACTH and cortisone. This section contains much useful and up-to-date information but one would wish for a more critical approach to therapy, omitting more of those forms of treatment which have been proved valueless or based on single case reports. Dr. Wiener includes numerous diet menus against which the average British patient would revolt; for example, he suggests a diet of 1 quart of milk and 1 quart of water per day for acute contact dermatitis. The Schroth thirst cure for eczema which appears in full in two places (page 183 and 527) sounds so appalling only the most hardy patient would survive.

Despite these criticisms, we should be grateful to Dr. Wiener for having compiled this book of reference which should find a place in our dermatological libraries.

I. B. S.

BRITISH ASSOCIATION OF DERMATOLOGY
THIRTY-SIXTH ANNUAL MEETING

The Thirty-sixth Annual Meeting of the Association is to be held in London under the presidency of Dr. G. B. Dowling, on 18 and 19 July, 1956. The principal subjects for discussion will be "Purpura" and "Drug Eruptions".

FRANCO-BRITISH MEETING

This meeting, the counterpart of the Franco-British Meeting held in Paris in 1954, will be held in London on 20 and 21 July, 1956.

Particulars of the detailed arrangements of these meetings will be circulated in due course.

* *Systemic Associations and Treatment of Skin Diseases*, KURT WIENER, M.D. (1955). London: Henry Kimpton. Pp. 556. Illus. 90. Price £6. 6s. 0d.

CURRENT LITERATURE

THE ATTACK OF CHEMICALLY MODIFIED KERATIN BY CERTAIN DERMATOPHYTES.

A. J. E. BARLOW and F. W. CHATTAWAY. (1955) *J. invest. Derm.*, **24**, 65.

The resistance of hair to attack is reduced by treatment with thioglycollic acid (which is supposed to break disulphide bonds), sodium metabisulphate (same, plus disorientation of fibre structure), and lithium bromide (breaks hydrogen bonds). It is increased by mercuric acetate and benzoquinone (cross linking free amino group), diepoxybutane (carboxyl groups), ninhydrin and dibromopropane (which forms trimethylene bridges between sulphur atoms in adjacent molecules). The last treatment completely inhibited all the fungi used in the experiment. The hair was, of course, well washed between treatment and inoculation in order to exclude the direct influence of the reagent, but in no case—not even in that of untreated hair—did the fungus attack the hair in exactly the same way as it does in nature, nor was fluorescence produced.

All sorts of anatomical and therapeutic possibilities are brought out in this most interesting paper. J. H. T. D.

THERAPEUTIC ASSAY OF TOPICALLY APPLIED 9a-FLUORHYDROCORTISONE ACETATE IN SELECTED DERMATOSES. V. H. WITTEN, M. B. SULZBERGER, E. H. ZIMMERMAN and A. J. SHAPIRO. (1955) *J. invest. Derm.*, **24**, 1.

A symmetrical paired comparison of the salt with the free alcohol but without control by facsimile dummy. Any advantage to the salt was probably no more significant than the general impression that 0.2% preparations were more effective than 0.1% ones. The diagnosis in 28 out of the 62 cases was atopic dermatitis and in 7 allergic contact dermatitis, the others miscellaneous dermatoses.

"The reasons why the hydrocortisone free alcohol in the relatively low concentrations (down to 0.1%) in the vehicles used appeared to be so effective in many of the cases must be the object of further investigation." J. H. T. D.

MELANIN FORMATION IN VITILIGINOUS SKIN UNDER THE INFLUENCE OF EXTERNAL APPLICATION OF 8-METHOXYSPOALEN. N. B. KANOF. (1955) *J. invest. Derm.*, **24**, 5.

Of 85 cases of vitiligo treated 32 produced new pigment, but in only 6 cases was the result cosmetically worthwhile.

Symmetrical paired comparisons were used in this experiment.

Although the author confirms *in vitro* findings that the drug strongly absorbs most of the radiation to which it is supposed to condition the pigmentary function of the skin, and believes it to penetrate the skin, exposures to light were in all cases made immediately after application: and no attempt was made to try the effect of washing it off after giving time for its absorption and before exposure.

Sunlight was more effective than either hot quartz or carbon arc light, but severe reactions took place even when the erythematogenic (below 3200 Å) part of the spectrum was excluded by a filter. But neither repigmentation nor erythema could be obtained with the drug or with light alone. The two reactions appeared to be unconnected. J. H. T. D.

LIPOIDOSES.

(1954). *Bull. Soc. franc. Derm. Syph.*, **5**, 399–478.

This is an account of a four-day meeting at Toulouse devoted to lipid diseases and allied conditions. Current ideas on xanthomatosis are surveyed by Nanta, on essential hyperlipaemia by Gadrat and on xanthogranulomatosis (a wide term including conditions varying from lipid deposits in inflammatory lesions to Hand-Schüller-Christian disease) by Bazex. Other contributions include an important study by Pautrier and Wöringer on lipomelanotic reticulosis. The whole account is too long to be summarized, but is a valuable survey of a wide field. F. F. H.

HYPERKERATOSIS FOLLICULARIS ET PARAFOLLICULARIS IN CUTEM PENETRANS (KYRLE). J. GOMEZ ORBANEJA and P. A. QUINONES. (1955) *Actas dermo-sif. Madrid*, 46, 237.

The most interesting feature of this case is that in some sections the horny plug is in direct contact with the corium and in others there is an intermediate layer of epidermal cells. The patient also had hypothyroidism, hepatic insufficiency and a low content of vitamin A in the blood. She responded well to thyroxin and injections of vitamin A.

G. W. B.

KERATOACANTHOMA. N. PUENTE DUANY. (1955) *Arch. cubanos Cancerología*, 14, 24.

The author reviews the literature and describes 19 cases of his own, of which 17 showed senile changes of the skin. In addition to keratoacanthoma 90% of his patients had basal cell epithelioma of the skin or other organ; 5 had adenoacanthoma and the author thinks that there is a close connection between the two conditions. Sometimes the histology of what is clinically a typical keratoacanthoma shows a variety of conditions.

G. W. B.

PSEUDOMELANOMATOUS HAEMOSIDERIN HISTIOCYTOMA OF DISS. D. ARGÜELLES-CASALS. (1955) *Arch. cubanos Cancerología*, 14, 95.

A hard pigmented pea-sized tumour had been present on the leg of a woman, aged 24, for eighteen months. Histologically there were fusiform polyhedral and star-shaped cells with abundant protoplasm, and also multinucleate giant cells. Masses of haemosiderin were seen in some cells and in the interstitial tissue, particularly on the periphery.

G. W. B.

HYPOPHYSEAL IMPLANTATION IN CHRONIC DERMATOSES. W. KÜHNAT. (1954) *Z. Haut-u. Geschlkr.*, 16, 46.

Results in 102 patients were surprisingly good, with occasional permanent cure in psoriasis, chronic endogenous eczema and pruritus vulvae. A second implant was necessary in only 6 cases.

P. D. C. K.

PFEIFER-WEBER-CHRISTIAN DISEASE AND TRAUMATIC PANNICULITIS. H. STUHLERT. (1954) *Z. Haut- u. Geschlkr.*, 16, 321.

Report on one case. Node formation can be produced either by an allergic reaction to a focal toxic irritant or by trauma.

P. D. C. K.

TREATMENT OF SALVARSAN DERMATITIS WITH FOLIC ACID. W. FLÖTER. (1954) *Z. Haut-u. Geschlkr.*, 17, 67.

Of 18 cases treated, 17 responded favourably in a relatively short time. The benefit is attributed either to an antiallergic action of the folic acid, or to a general antitoxic effect.

P. D. C. K.

CATERPILLAR DERMATITIS. J. KOHLER. (1954) *Z. Haut-u. Geschlkr.*, 17, 180.

An unusual form of dermatitis arising among workers in contact with wood. Hair from a caterpillar *Thaumetopea processionea* is the irritant. Hairs and skin are shed in nests in the wood, especially oak.

A papular dermatitis affects the neck, chest and axillae. Five cases are described.

P. D. C. K.

INDUSTRIAL DERMATITIS. E. LANGER and H. KRÜGER (1954) *Z. Haut-u. Geschlkr.*, 17, 227.

Of 678 persons said to be suffering from dermatitis of industrial origin, 270 gave a positive reaction to patch tests; 20.4% of these were in medical or allied professions, 17.8% bakers, 14.4% engineers, 11% painters and 10% hairdressers.

P. D. C. K.

SARCOMA ARISING ON LUPUS ERYTHEMATOSUS W. GRASSREINER and R. STERBA. (1954) *Z. Haut-u. Geschlkr.*, 17, 304.

A spindle cell sarcoma arising on patches of chronic lupus erythematosus. Picture and photomicrograph. The authors claim that this is only the second case to be recorded.

P. D. C. K.

CHEILITIS GRANULOMATOSA (MIESCHER). H. GROMZIG and G. KUNISS. (1953) *Z. Haut- u. Geschlkr.*, **15**, 9.

Three cases each regarded as a *forme fruste* of the Melkersson-Rosenthal syndrome (recurrent swelling of the lips, later constant, lingua plicata, facial nerve palsy). Histology was typically tuberculoid, but animal inoculation negative. Two cases had a Mantoux reaction positive to 1 : 5,000, no sarcoidosis elsewhere.

Wedge-shaped excision of the hypertrophied tissue is recommended.

P. D. C. K.

INTERNAL THERAPY OF BENIGN INFECTIOUS EPITHELIOSES. W. HARTMANN. (1955) *Derm. Wschr.*, **131**, 505.

In his search for a simple treatment of warts the author discovered that a combination of extract of *Thuja* and of *Artemisia abronatum* given in doses of 10 minims of each three times a day made warts disappear in a higher proportion than could be expected as a result of suggestion according to the figures of various authors. It was also possible to bring about a disappearance of the lesions in 6 out of 7 cases of molluscum contagiosum. In this disease it has never been suggested that spontaneous healing occurred.

The author believes that peripheral vascular abnormalities contribute to the formation of warts. Many patients showed acrocyanosis, had low blood pressures, tended to have cold and moist hands and often suffered from hyperidrosis. Tincture of abronatum is supposed to counteract these abnormalities and in a number of cases a rise in skin temperature could be observed under treatment.

W. G. T.

SYMPTOMATIC ERYTHEMA MULTIFORME IN MILKER'S NODES AND TULARAEMIA. H. LANGHOFF. (1955) *Derm. Wschr.*, **131**, 520.

Eleven cases of erythema multiforme occurring about two weeks after the development of milker's nodes are reported. The cause of this secondary eruption could not be established.

Four cases of tularaemia occurred in a family. All affected showed an erythema multiforme at the height of infection—of which it forms part, since organisms could be isolated from vesicular lesions.

W. G. T.

ARTERIOVENOUS ANASTOMOSES IN KLIPPEL-TRENAUNAY'S SYNDROME. R. PEISTER and K. BÄTZNER. (1955) *Derm. Wschr.*, **131**, 537.

The syndrome (also haemangiectatic hypertrophy of Parkes-Weber) is characterized by a combination of a "naevus" of varying extent with enlargement of the affected limb. The picture is probably less rare than was thought in the past. Usually the lower limb is affected, sometimes the hand and more rarely the arm. A case is described and the paper contains an excellent picture of the normal and affected leg. Arteriography showed the filling of a number of tortuous veins which can only have occurred through arterio-venous anastomoses, since no veins were seen in the lower limb in pictures taken during injection of the contrast material into the exposed femoral artery. A cystic translucency of the tibia was an additional abnormality.

W. G. T.

EPIDERMOLYSIS BULLOSA ET ALBO-PAPULOIDEA (PASINI). H. GÖTZ and K. MEINCKE. (1955) *Derm. Wschr.*, **131**, 481.

This condition was first described by Pasini in 1928 and since then only 30 other cases could be found in the literature. It is a variant of the classical form of epidermolysis bullosa, but seems to have a greater tendency to affect tissues of mesenchymal origin.

The authors report a patient, aged 22, who had shown typical lesions of epidermolysis bullosa from the age of 9 months. In later childhood she developed numerous white lesions on her trunk and when she came under observation showed both types of lesions.

Treatment with Germanin resulted in great improvement, particularly of the deformities of the finger- and toe-nails. Whereas it was possible to produce bullae by friction in areas where scars indicated previous active lesions, this was no longer possible after this treatment.

The formation of bullae in this disease is considered to be due to a hyaluronic acid-hyaluronidase imbalance and Germanin is thought to inhibit the action of hyaluronidase. The albo-papuloid lesions were unaffected by this treatment.

W. G. T.

REGIONAL DIFFERENCES OF THE TONUS OF CUTANEOUS VESSELS. W. SCHULZE and D. PAGEL. (1955) *Derm. Wschr.*, **131**, 488.

The authors establish threshold values for the development of an erythema after application of a solution of the tetrahydrofurfurylester of nicotinic acid to various parts of the skin. The lowest threshold values were found on the forehead, and these values increased in the order chest, arm, forearm, back, thigh and leg.

Further they found that there was a considerable variation in the time reactions took to develop after application of a standard concentration of this ester to the skin of the chest and abdomen. Reactions developed soonest in the region of the first rib and took longer to appear as the umbilical region was approached. The same results were obtained on the back and proved that vascular tonus increased with approach to the feet.

By this method disturbances of vascular function could be demonstrated in a child with a meningocele who showed no reactions on its paralysed limbs, whereas reactivity was greatly increased on the sixth thoracic segment of a tabetic.

W. G. T.

IDIOPATHIC HYPERLIPAEMIA AND PRIMARY HYPERCHOLESTERAEMIC XANTHOMATOSIS. IV. EFFECTS OF PROLONGED ADMINISTRATION OF HEPARIN ON SERUM LIPIDS IN IDIOPATHIC HYPERLIPAEMIA. WALTER F. LEVER, FRANZ S. M. HERBST and NANCY A. HURLEY. (1955) *A.M.A. Arch. Derm. Syph.*, *Chicago*, **71**, 150.

V. ANALYSIS OF SERUM LIPOPROTEINS BY MEANS OF ULTRACENTRIFUGE BEFORE AND AFTER ADMINISTRATION OF HEPARIN. WALTER F. LEVER, FRANZ S. M. HERBST and MARY E. LYONS. (1955) *A.M.A. Arch. Derm. Syph.*, *Chicago*, **71**, 158.

The first three papers in this series were published in *J. invest. Derm.*

Part IV records the results of injection of heparin for from 2 weeks to 8 months in 5 patients. In all a considerable decrease in turbidity and lipid values of the serum occurred along with disappearance or decrease in size of cutaneous xanthomata. There was no untoward reaction to heparin.

Part V. There is an excess of lipoids of the higher S_f classes in the serum in idiopathic hyperlipaemia: heparin accelerates their physiological conversion into those of the lower S_f classes. In spite of this there is no evidence so far that heparin deficiency is an aetiological factor in this disease.

J. K.

LOCAL ACTION OF HEPARIN ON XANTHOMAS. THOMAS CORNBLEET. (1955) *A.M.A. Arch. Derm. Syph.*, *Chicago*, **71**, 172.

Injection of up to 1 ml. of heparin sodium solution (5000 U.S.P. units) within and under the lesions once or twice a week caused them to flatten and disappear.

J. K.

TRENDS IN SCABIES. ERVIN EPSTEIN. (1955) *A.M.A. Arch. Derm. Syph.*, *Chicago*, **71**, 192.

"Scabies has become a rarity in North America, in Western Europe, and in the Pacific Area as far west as Japan." The cause of this fall in incidence is unknown, but it is possible that the popularity of electric washing machines and synthetic detergents may have something to do with it.

J. K.

IS MYCOSIS FUNGOIDES AN ENTITY? SAMUEL M. BLUEFARB. (1955) *A.M.A. Arch. Derm. Syph.*, *Chicago*, **71**, 293.

The classical type as described by Alibert can be considered as mycosis fungoides. The *tumeurs d'emblée* type is usually lymphosarcoma or occasionally a primary manifestation of Hodgkin's disease, while the erythrodermatous form is a manifestation of lymphatic leukaemia.

J. K.

ELASTIC FIBRES IN UNUSUAL DERMATOSES. LOUIS H. WINER. (1955) *A.M.A. Arch. Derm. Syph.*, *Chicago*, **71**, 338.

Different types of elastic degeneration are seen in localized scleroderma and balanitis xerotica obliterans. Colloid milium is a massive degeneration of collagen, amorphous in character with Hotchkiss-McManus stains. Senile elastosis differs in having a reticulate pattern of its degenerated collagen. In Werner's syndrome and pseudoxanthoma elasticum the elastic fibres are increased, but in the former they do not have the "curlicue" conglomeration seen in the latter. Collagen in Werner's syndrome resembles that seen in senile elastosis.

J. K.

STUDIES ON SWEAT RETENTION IN VARIOUS DERMATOSES. FRANK E. CORMIA and VIRGINIA KUZKENDALL. (1955) *A.M.A. Arch. Derm. Syph., Chicago*, **71**, 425.

Sweat retention was studied in various eczematous conditions, in psoriasis and in hypertrophic lichen planus. The gland itself and the dermal portion of the duct were normal, and retention is caused by obstruction in the upper epidermal portion of the sweat duct. Where the sweat goes to is not clear. J. K.

SYSTEMATIC MAST-CELL DISEASE WITH URTICARIA PIGMENTOSA. EMMETT B. REILLY, JURO SHINTANI and JOSEPH GOODMAN. (1955) *A.M.A. Arch. Derm. Syph., Chicago*, **71**, 561.

From the study of one case and the literature the authors conclude that the mast-cell is controlled by the pituitary-adrenal system and that heparin (a product of the mast-cell) and procollagen (a product of the fibroblast) interact to form collagen. This may explain the association of the mast-cell with fibrous proliferation and the inflammatory response. J. K.

EFFECT OF QUINACRINE (ATABRINE) UPON LUPUS ERYTHEMATOSUS PHENOMENON. EDMUND L. DUBOIS. (1955) *A.M.A. Arch. Derm. Syph., Chicago*, **71**, 570.

Mepacrine inhibits L.E. cell formation *in vitro*.

J. K.

OBSERVATIONS ON PERIPHERAL CIRCULATION IN VARIOUS DERMATOSES. STANLEY E. HUFF. (1955) *A.M.A. Arch. Derm. Syph., Chicago*, **71**, 575.

Additional evidence of a vascular dysfunction in patients with scleroderma, psoriasis and lupus erythematosus (chronic discoid, acute and sub-acute systemic types) is seen in abnormal photoelectric plethysmograms of the fingers in these diseases compared with normal subjects and patients suffering from a variety of dermatoses including atopic dermatitis. These abnormalities occur in sites remote from visible lesions. J. K.

CUTANEOUS MANIFESTATIONS OF MYELOGENOUS LEUKAEMIA. MAURICE J. COSTELLO, ORLANDO CANIZARES, MEREDITH MONTAGUE and CONSTANCE MILETTI BUNCKE. (1955) *A.M.A. Arch. Derm. Syph., Chicago*, **71**, 605.

Four patients with myeloid leukaemia showed different skin lesions. One had ulcerating tumours; the second, generalized plaque-like lesions associated with pulmonary tuberculosis; the third, petechiae, haemorrhagic blotches and haemorrhagic bullae, while the fourth had a combination of these. Cortisone was of value in controlling the symptoms. J. K.

DIAGNOSTIC AND THERAPEUTIC ERRORS IN CERTAIN DERMATOSES OF THE VULVA. E. P. SCHOCH and C. H. MCCUITION. (1955) *J. Amer. med. Ass.*, **157**, 1102.

A further attempt to bring order out of confusion. The clinical and histological features of some dermatoses of the vulva are tabulated. Kraurosis and lichen sclerosus are considered to be the same process which can be the precursor of leucoplakia and which is labelled primary sclerosing atrophy. Other atrophies of the vulva are not regarded as preleucoplakic. The material on which these concepts are based is not described and although this article deserves to be read as a stimulus to further investigations the authors' views cannot be completely reconciled with the experience of most dermatologists. A. J. R.

OVERTREATMENT DERMATITIS. L. E. GAUL. (1955) *J. Amer. med. Ass.*, **157**, 720.

This review opens with an estimate of the incidence of overtreatment dermatitis in the United States which suggests that it is a much greater problem than in Britain. The organic mercurials, the sulphonamides, local anaesthetics, antihistamines and antibiotics are particularly common offenders. Diagnosis and prevention are discussed, and there is a useful bibliography. Some instructive case histories are included. A. J. R.

CLINICAL FEATURES, PATHOLOGY, AND THERAPY OF HAEMOCHROMATOSIS. M. S. KLECKNER *et al.* (1955) *J. Amer. med. Ass.*, **157**, 1471.

The literature on haemochromatosis is reviewed and the findings in 46 cases are summarized. Three types are recognized; primary haemochromatosis, a familial type and a type associated with a chronic refractory anaemia. The first two types occur predominantly in men in the fifth or sixth decades and death results from hepatic insufficiency or cardiac failure after an average

course of four years. The third type occurs in young adults of either sex and is fatal in about five years, and should be treated by multiple transfusions in contrast to the frequent blood-letting indicated in the primary types.

A. J. R.

METASTATIC CARCINOMA OF THE UMBILICUS. H. M. SCHIEBEL *et al.* (1955) *J. Amer. med. Ass.*, **157**, 1489.

Five cases of metastatic carcinoma of the umbilicus are reported. A nodule in the umbilicus may be the only abnormal physical finding in a patient with intra-abdominal carcinoma.

A. J. R.

BORON ABSORPTION FROM BORATED TALC. R. S. FISHER *et al.* (1955) *J. Amer. med. Ass.*, **157**, 503.

Boric acid poisoning can be diagnosed only by the estimation of boric acid in the blood or tissues, as boron is present in fruits and other foods and a merely qualitative demonstration of boric acid in the urine may have no clinical significance. No increased concentration of boron could be demonstrated in the blood of a large series of infants on whom a boric acid dusting powder had been freely used for a year. No authenticated case of boric acid poisoning from borated talc could be found in the literature.

A. J. R.

SUCCESSFUL HOMOGRAFT OF SKIN IN A CHILD WITH AGAMMAGLOBULINAEMIA. R. A. GOOD and R. L. VARCO. (1955) *J. Amer. med. Ass.*, **157**, 713.

The success of a homograft in a child with agammaglobulinaemia lends support to the concept that the customary failure of homografting is the result of an immunological mechanism.

A. J. R.

CHLOROQUINE IN TREATMENT OF LICHEN PLANUS AND OTHER DERMATOSES. S. AYRES III and S. AYRES, JR. (1955) *J. Amer. med. Ass.*, **157**, 136.

Chloroquine appeared to be effective in some, but not all, cases of lichen planus and of warts. It was of no value in psoriasis. The number of cases treated was too small for the results to be significant. There were several cases of severe dermatitis medicamentosa and one of methaemoglobinemia.

A. J. R.

CONTACT DERMATITIS FROM CHLORPROMAZINE. G. M. LEWIS and H. H. SAWICKY. (1955) *J. Amer. med. Ass.*, **157**, 909.

Two nurses in repeated contact with chlorpromazine in the course of administering intramuscular injections of the drug developed contact dermatitis which was of exceptionally long duration.

A. J. R.

HIRSUTISM A MANIFESTATION OF JUVENILE HYPOTHYROIDISM. W. H. PERLOFF. (1955) *J. Amer. med. Ass.*, **157**, 651.

The author briefly reports four cases and mentions two others in which children with hypothyroidism developed hirsutism of the back and shoulders, the outer aspects of arms and legs, and the sides of the face. Complete or almost complete recovery took place after 6-8 months of treatment with thyroid.

A. J. R.

CORRELATION OF FIELD SIZE AND CANCEROCIDAL DOSE IN X-RAY TREATMENT OF SKIN CANCER. K. D. A. ALLEN and J. H. FREED. (1955) *J. Amer. med. Ass.*, **157**, 1271.

The range of safe dosage in the treatment of skin cancer diminishes as the size of the field increases. The minimum curative dose for a very small field is above that which the normal skin will tolerate when very large fields are used. In an average group of cases the ideal dose is the average between the maximum normal skin tolerance and the minimum curative dose for the particular size of field. However, other factors need consideration in the individual case, particularly the age of the patient and the site of the lesion. In the elderly a dose near the maximum normal skin tolerance may result in delayed healing, radiodermatitis or necrosis. On the back of the hand, where the collateral blood supply is relatively poor even the minimum curative dose may be too much and plastic surgery is preferable.

A. J. R.

USE OF FLUDROCORTISONE ACETATE IN DERMATOSES. R. C. V. ROBINSON. 1955. *J. Amer. med. Ass.*, **157**, 1300.

Fludrocortisone acetate is a derivative of hydrocortisone. Preliminary trials indicated that in ointments or lotions this drug is effective in concentrations as low as 0.1%. Administered orally to two patients fludrocortisone had about 25 times the therapeutic potency of cortisone. If these findings are confirmed the greater economy will be an advantage. A. J. R.

DERMATOSES DUE TO OILS USED IN INDUSTRY. Committee on Occupational Dermatoses. (1955) *J. Amer. med. Ass.*, **157**, 1611.

An informative review article in which clinical features, differential diagnosis and prevention are considered. A. J. R.

TREATMENT OF HERPES ZOSTER WITH GAMMA GLOBULIN. J. I. WEINTRAUB. 1955. *J. Amer. med. Ass.*, **157**, 1611.

Six patients with herpes zoster were treated with gamma globulin. One received an initial dose of 20 c.c., but the others were given 10 c.c., followed by 5 c.c. on alternate days. In four there was relief of pain within 24 hours and no further progression of the skin lesions. A. J. R.

PITFALLS OF THE SKIN TEST IN ALLERGY. M. MURRAY PESHKIN. (1955) *J. Amer. med. Ass.*, **157**, 820.

The author of this article clearly places more reliance on skin testing in eczema and urticaria and in asthma than the majority of dermatologists in this country. He is here concerned with some of the practical problems encountered in the performance and interpretation of skin tests, and of these he gives a good account. A. J. R.

PROBLEMS OF DRUG ALLERGY. E. A. BROWN. (1955) *J. Amer. med. Ass.*, **157**, 814.

In this stimulating paper a well-known allergist discusses the theoretical problems of drug eruptions, and in particular the mechanisms involved. He points out that relatively few of the large number of case-reports of drug reactions are sufficiently detailed to be of value. There is much too great a delay in the publication of reactions to new drugs. A. J. R.

LONG TERM TREATMENT OF LEPROSY WITH CORTISONE. E. C. DEL POZO, A. G. OCHOA, S. R. VENEGAS, M. MARTINEZ-BAEZ and M. ALCARAZ. (1955) *J. invest. Derm.*, **24**, 51.

Of the 9 patients in whom it proved possible to suppress a more or less continuous lepra-reaction by means of a daily dose of 25 to 150 mg. of cortisone only 4 successfully completed the experiment, one purpose of which was to ascertain the general physiological effects of prolonged cortisone therapy.

Apart from making possible, in some of the cases, treatment with D.D.S., administration of which in 2 previously recalcitrant cases it was possible to continue after the end of the cortisone—the hormone itself appeared to do good: for patients not being treated with D.D.S. also improved. The authors discuss the possibility of this improvement being due to factors other than a mere suppression of the lepra-reaction. J. H. T. D.

A SILVER IMPREGNATION METHOD FOR PERIPHERAL NERVE ENDINGS. R. K. WISSELMANN. (1955) *J. invest. Derm.*, **24**, 57.

The author claims several advantages for his particular area-silver method, including constancy of results and not too exacting a technique. J. H. T. D.

ISOLATION OF A PLEUROPNEUMONIA-LIKE ORGANISM FROM A SKIN LESION ASSOCIATED WITH A FUSOSPIROCHAETAL FLORA. M. REITER and H. M. M. WENTHOLD. 1955. *J. invest. Derm.*, **24**, 31.

From the septic umbilicus of an obese syphilitic woman of 45 and from what was called a 'marked vaginal fluor' in the same case, were recovered two distinct organisms of this type. J. H. T. D.

STUDY OF SEVERAL FACTORS INFLUENCING CONTACT IRRITATION AND SENSITIZATION.E. M. ROCKWELL. (1955). *J. invest. Derm.*, **24**, 35.

Guinea-pigs sensitized to 2,4-DNCB and challenged with graded dilutions of antigen were used to assess the influence, on sensitization phenomena in the skin, of atmospheric temperature and humidity, pregnancy, ingestion of Fowler's solution and of mechanical damage.

Sufferers from prescribed industrial disease are not, of course, guinea-pigs; but the findings here should make some of us think twice before prescribing the traditional "clean light work in a cool dry place away from known irritants" especially if there is any intention of prognosing a time limit to the "loss of resistance".

J. H. T. D.

SOME EXPERIMENTS WITH ELECTROPHORETIC PATCH TESTS. H. HAXTHAUSEN. (1955)*J. invest. Derm.*, **24**, 211.

The shorter duration of the test exposure makes it possible not only to watch the entire course of events but to ascertain the effect of all kinds of local influences at all stages in the reaction. What limits the size of the test area to 3 cm. diameter is not clearly stated.

Freezing with CO₂ snow or ethyl chloride, heat, and U.V.R. have an inhibiting action which is "not quite constant though demonstrable in most cases".

Neither x-rays nor β -rays whether applied before or after had any effect. If lymphocytes play any part in a positive patch test reaction, P³² in application throughout the whole experiment should have had some effect, but it didn't.

Alkalies, acids and the salts of most heavy metals were effective only insofar as they damaged the skin. Arsenic, however, injected intradermally, though provocative in control of only the slightest redness, substantially inhibited the eczematoid reaction. Other substances reported to influence enzyme systems—such as vesicants, HCN, sodium salicylate, vitamin C, heparin, eserine, glutathione—had no effect.

Antihistamines, whether introduced simultaneously by electrophoresis or applied afterwards in the form of ointments, gave negative results, indicating "that the inhibitory effect in the eczematous allergic reaction that many clinicians still ascribe to these substances can hardly be a reality".

Hydrocortisone ointment failed except in one or two experiments in which it was used in a carbowax base. General clinical experience has, of course, shown that this hormone does not penetrate very well and is only commonly useful on anus, lips and eyelids. But once the skin becomes eczematized hydrocortisone ointment seems to accelerate healing. Injected intradermally however it was potent; not always in inhibition, sometimes only accelerative of healing. It does not interfere with the reaction to CO₂ snow, though erythema actinica is partly inhibited. The effects of tar, hydroxyquinoline, chrysarobin or other supposedly anti-eczematous drugs were not investigated.

J. H. T. D.

ON THE RELATIVE ADEQUACY OF SOME AMERICAN CHAMBERS FOR MEASUREMENT IN THE GRENZ RAY RANGE. V. H. WITTEN, E. N. GRISEWOOD and E. OSBRY. (1955)*J. invest. Derm.*, **24**, 365.

"Among the reasons for the increasing use of grenz radiation are: (1) availability of the units, (2) improvements in their construction, (3) improvements in the tubes, notably the introduction of beryllium windows, and (4) greater knowledge of the indications for the use and the results to be expected with this mode of therapy." Waning confidence in x-rays or the accumulating proof of its impotence are not mentioned.

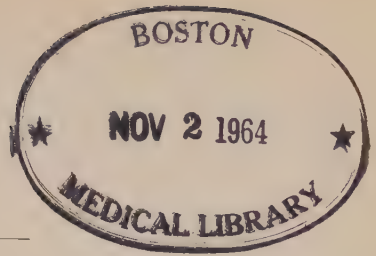
Since the side effects of this form of radiation (which has, after all, been used here and there for more than 30 years) are quite conspicuous, and since it is just as well to know what one is supposed to be doing; here is all we need to know when buying a gadget to measure the dose.

J. H. T. D.

ACRODERMATITIS ENTEROPATHICA SUCCESSFULLY TREATED WITH DIODOQUIN. D.BLOOM and N. SOBEL. (1955) *J. invest. Derm.*, **24**, 67.

Although the question whether this rare syndrome is a congenital-developmental dystrophy akin to epidermolysis bullosa, a monilia infection or some effect of intestinal infestation with *lamblia*, is not precisely answered by this additional success with an intestinal antiseptic containing iodine which is said not to be absorbed; it is here attractively presented with lucid argument.

J. H. T. D.



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*Made and printed in Great Britain for
H. K. Lewis & Co. Ltd., by
Adlard & Son, Ltd., at their works, Bartholomew Press, Dorking.*

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